NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 414

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PENTACHLOROANISOLE

(CAS NO. 1825-21-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. BOX 12233
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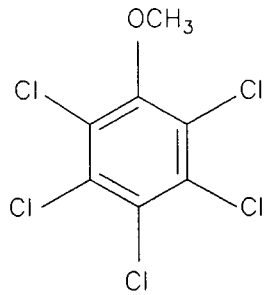
ABSTRACT



PENTACHLOROANISOLE

CAS No. 1825-21-4

Chemical Formula: $C_7H_3Cl_5O$ Molecular Weight: 280.5

Synonyms: 2,3,4,5,6-pentachloroanisole; methyl pentachlorophenate; methyl pentachlorophenyl ether; *o*-methylpentachlorophenol; pentachloromethoxybenzene; pentachlorophenyl methyl ether

Pentachloroanisole is a chlorinated aromatic compound which is widely distributed at low levels in the environment and in food products. Formation of pentachloroanisole in the environment may result from the degradation of structurally related, commercially important, ubiquitous chlorinated aromatic compounds such as pentachlorophenol and pentachloronitrobenzene which are known rodent toxins or carcinogens. Toxicology and carcinogenesis studies were conducted by administering pentachloroanisole (>99% pure) in corn oil by gavage to groups of male and female F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* strains, mouse lymphoma cells, and Chinese hamster ovary cells.

16-Day Studies in Rats

Groups of five male and five female F344/N rats were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 16 days at doses of 0, 100, 125, 150, 175, or 200 mg/kg body weight. Deaths occurred during days 2 and 3 in rats receiving doses of 125 mg/kg or greater; these deaths were considered directly related to pentachloroanisole administration. No biologically significant changes in mean body weight gains or final body weights were noted in the 100 mg/kg groups of rats. Because of the high early mortality rate, valid comparisons of body weight differences in other dose groups could not be made. Inactivity was noted in all dose groups. Rats administered doses of 125 mg/kg or greater also exhibited dyspnea.

16-Day Studies in Mice

Groups of five male and five female B6C3F$_1$ mice were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 16 days at doses of 0, 100, 175, 250, 325, or 400 mg/kg. Deaths occurred during days 2 and 3 in mice receiving doses of 175 mg/kg or greater; these deaths were considered directly related to chemical administration. No biologically significant changes in mean body weight gains or final body weights were noted in 100 mg/kg males or 100 or 175 mg/kg females. Because of the high early mortality rate, valid comparisons of body

weight differences in other dose groups could not be made. Inactivity was noted in dosed mice.

13-Week Studies in Rats

Groups of 10 male and 10 female rats were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 13 weeks at doses of 0, 40, 80, 120, 140, or 180 mg/kg body weight. Most rats receiving doses of 120 mg/kg or greater died during the first week of the study as a direct result of pentachloroanisole administration.

Mean body weight gains of males administered 40 or 80 mg/kg and of females administered 40, 80, or 120 mg/kg pentachloroanisole were significantly lower than those of the controls. Most dosed rats exhibited temporary inactivity for several hours after dosing. Relative liver and kidney weights of males administered 40 or 80 mg/kg and absolute and/or relative liver and kidney weights of females administered 40 to 120 mg/kg were significantly greater than those of the controls.

Lesions observed in males administered 80 mg/kg or more and in females administered 120 mg/kg or more included pulmonary congestion, hemorrhage, and/or edema, meningeal congestion, and hepatocellular necrosis, glycogen depletion, and degeneration of biliary epithelium in the liver.

13-Week Studies in Mice

Groups of 10 male and 10 female mice were administered pentachloroanisole in corn oil by gavage once per day, 5 days per week, for 13 weeks at doses of 0, 40, 80, 120, 140, or 180 mg/kg body weight. Most mice administered doses of 120 mg/kg or higher died during the first week of the study as a direct result of pentachloroanisole administration.

Mean body weight gains of females administered 40 to 140 mg/kg were significantly greater than that of the controls, but those of dosed males were similar to that of the controls. Most dosed mice exhibited temporary inactivity for several hours after dosing. Absolute and relative liver weights of males administered 80 mg/kg, absolute and relative liver weights of females administered 40 to 180 mg/kg, and absolute and relative kidney weights of females administered 80 to 180 mg/kg pentachloroanisole were also significantly greater than those of the controls.

Lesions observed in males administered 40 mg/kg or more and in females administered 80 mg/kg or more included pulmonary congestion and/or edema, adrenal congestion, lymphoid depletion of lymph nodes and thymus, hepatocellular cytomegaly and karyomegaly, and pigment accumulation in hepatocytes and Kupffer cells.

2-Year Studies in Rats

Based on the chemical-related mortality and liver lesions seen in the 16-day and 13-week studies, doses selected for the 2-year studies were 0, 10, 20, and 40 mg/kg for males and 0, 20, and 40 mg/kg for females. Groups of 70 male and 70 female rats were administered pentachloroanisole in corn oil by gavage 5 days per week for up to 2 years. At 9 and 15 months, up to 10 animals per group were selected for interim evaluations.

Survival, Body Weights, and Clinical Findings

The survival of high-dose males was significantly decreased (vehicle control, 24/50; low-dose, 20/50; mid-dose, 24/50; high-dose, 14/50); most deaths in the high-dose group occurred at or before week 16. The majority of deaths in the mid- and high-dose groups may have been due to pentachloroanisole-related hyperthermia. The survival of dosed females was greater than that of the controls (29/50, 35/50, 44/50). Final mean body weights of mid- and high-dose males were 7% and 10% lower than that of the controls; final mean body weight of high-dose females was 11% lower than that of the controls. Final mean body weights of other dose groups were similar to those of the vehicle controls. At the 9-month interim evaluation, mean rectal temperature of males administered 40 mg/kg was significantly greater than that of the controls. Relative liver and kidney weights of males and females administered 20 or 40 mg/kg were significantly greater than those of controls. At the 15-month interim evaluation, relative liver weights of dosed females and absolute liver weights of 40 mg/kg females were significantly greater than those of the controls, as were relative liver and kidney weights of 40 mg/kg males.

Pathology Findings

In the 2-year studies, administration of pentachloroanisole to males was associated with significant increases in the incidences of benign adrenal medulla pheochromocytomas. The incidence of benign

adrenal medulla pheochromocytomas was marginally increased in high-dose females and slightly exceeded the range of the historical controls. Incidences of adrenal medulla hyperplasia were increased in dosed female rats, but not in dosed males. The incidences of pancreatic adenomas and focal hyperplasia were decreased in dosed males. The incidences of mammary gland fibroadenomas and uterine stromal polyps and sarcomas (combined) were decreased in high-dose females. Treatment-related increased incidences of intracytoplasmic pigmentation occurred in renal tubule epithelium, olfactory epithelium, and hepatocytes of males and females. Congestion and hemorrhage of the lungs, lymph nodes, thymus, adrenal cortex, and meninges, as well as hepatocellular centrilobular necrosis occurred almost exclusively in mid- and high-dose males that died or were killed moribund before the end of the studies.

2-Year Studies in Mice

Based on the chemical-related mortality and liver lesions seen in the 16-day and 13-week studies, doses selected for the 2-year studies were 0, 20, and 40 mg/kg. Groups of 70 male and 70 female mice were administered pentachloroanisole in corn oil by gavage 5 days per week for up to 2 years. At 9 and 15 months, up to 10 animals per group were selected for interim evaluations.

Survival, Body Weights, and Clinical Findings

The survival of dosed males was similar to that of the controls; survival of high-dose females was lower than that of the controls (24/50, 25/50, 16/50). The decreased survival of the high-dose females was attributed primarily to ovarian abscesses which were observed after moribund sacrifice. At the 9-month interim evaluation, the mean body weight of males administered 40 mg/kg was significantly lower than that of the vehicle controls. Absolute and relative liver weights of females and the relative liver weight of males administered 40 mg/kg were significantly greater than those of the controls. Final mean body weights of low- and high-dose males were 11% and 17% lower than that of the controls. Final mean body weights of dosed females were similar to that of the controls. There were no clinical findings attributed to pentachloroanisole administration.

Pathology Findings

Centrilobular hepatocyte cytomegaly and pigment accumulation in hepatocytes and Kupffer cells were seen in dosed mice, but not in controls at the 9- and 15-month interim evaluations. In the 2-year studies, the incidence of benign pheochromocytomas was significantly increased in high-dose males. Dosed males also exhibited increased incidences of adrenal medulla hyperplasia and hypertrophy. The incidences of hemangiosarcomas of the liver were significantly increased in dosed males. Increased incidences of hepatocellular cytologic alteration, biliary tract hyperplasia, and Kupffer cell pigmentation occurred in dosed males and females; the incidences of mixed cell foci were also increased in dosed males. Cytologic alteration encompassed hepatocellular cytomegaly, karyomegaly, hepatocyte degeneration and necrosis, and multinucleated giant cell formation, and was considered an advanced stage of the pathologic process observed at 13 weeks.

Genetic Toxicology

Pentachloroanisole was mutagenic in *Salmonella typhimurium* strains TA98 and TA1537 in the absence but not in the presence of exogenous metabolic activation (S9). No clear mutagenic activity was observed in TA100 with hamster S9, without S9, or in TA1535 with or without S9. An equivocal response was observed in TA100 with rat S9. Pentachloroanisole was positive for induction of trifluorothymidine resistance in mouse lymphoma L5178Y cells with S9; the response observed without S9 was weak and inconsistent. In cytogenetic tests with Chinese hamster ovary cells, pentachloroanisole induced sister chromatid exchanges, but not chromosomal aberrations, with and without S9.

Toxicokinetics

Male and female F344/N rats and B6C3F$_1$ mice were administered 10, 20, or 40 mg/kg pentachloroanisole by gavage or 10 mg/kg pentachloroanisole intravenously (Appendix H). A rapid elimination of pentachloroanisole and a rapid formation of its main metabolite, pentachlorophenol, were seen in both species after an intravenous or an oral dose of pentachloroanisole. The area under the concentration-versus-time curve of pentachloroanisole increased with dosage in each species but the dose proportionality was lost above 20 mg/kg. No sex-related differences were found in the rate of absorption of pentachloroanisole from the GI tract, in the area under the concentration-versus-time curve, or in the overall rate elimination of pentachloroanisole. However, in female rats the area

under the concentration-versus-time curve of pentachlorophenol was significantly larger than in male rats. No such difference was observed in mice.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of pentachloroanisole in male F344/N rats based on increased incidences of benign pheochromocytomas of the adrenal medulla. There was *equivocal evidence of carcinogenic activity* of pentachloroanisole in female F344/N rats based on marginally increased incidences of benign pheochromocytomas of the adrenal medulla. There was *some evidence of carcinogenic activity* of pentachloroanisole in male $B6C3F_1$ mice based on increased incidences of benign pheochromocytomas of the adrenal medulla and hemangiosarcomas of the liver. There was *no evidence of carcinogenic activity* of pentachloroanisole in female $B6C3F_1$ mice given doses of 20 or 40 mg/kg.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia in female rats and increased incidences of pigmentation in the renal tubule epithelium, olfactory epithelium, and hepatocytes of male and female rats. In addition, decreased incidences of pancreatic adenomas and focal hyperplasia in male rats and decreased incidences of mammary gland fibroadenomas and uterine stromal polyps and sarcomas (combined) in female rats were observed. Hyperthermia-related lesions in male rats receiving 20 or 40 mg/kg were considered indirectly related to pentachloroanisole administration.

Pentachloroanisole administration was associated with increased incidences of adrenal medulla hyperplasia and hypertrophy and hepatocellular mixed cell foci in male mice. In male and female mice, nonneoplastic liver lesions associated with pentachloroanisole administration included hepatocellular cytologic alteration, Kupffer cell pigmentation, biliary tract hyperplasia, and subacute inflammation.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pentachloroanisole

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 10, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage	0, 20, or 40 mg/kg in corn oil by gavage
Body weights	Mid- and high-dose groups lower than vehicle controls	High-dose group lower than vehicle controls	Dosed groups lower than vehicle controls	Dosed groups similar to vehicle controls
2-Year survival rates	24/50, 20/50, 24/50, 14/50	29/50, 35/50, 44/50	30/50, 27/50, 28/50	24/50, 25/50, 16/50
Nonneoplastic effects	Pigmentation: renal tubule epithelium (1/50, 23/50, 22/50, 16/50); olfactory epithelium (0/50, 29/50, 40/50, 25/50); hepatocytes (0/50, 0/50, 1/50, 4/50)	Adrenal medulla: hyperplasia (10/50, 18/50, 25/50) Pigmentation: renal tubule epithelium (0/50, 43/50, 45/50); olfactory epithelium (0/49, 46/50, 50/50); hepatocytes (0/50, 18/50, 24/50)	Adrenal medulla: hyperplasia (0/50, 13/50, 29/48); hypertrophy (0/50, 3/50, 36/48) Liver: cytologic alteration (0/50, 50/50, 50/50); Kupffer cell pigmentation (1/50, 50/50, 50/50); biliary tract hyperplasia (0/50, 47/50, 48/50); subacute inflammation (0/50, 49/50, 49/50); mixed cell foci (9/50, 15/50, 27/50)	Liver: cytologic alteration (1/50, 34/50, 39/50); Kupffer cell pigmentation (0/50, 37/50, 48/50); biliary tract hyperplasia (1/50, 16/50, 30/50); subacute inflammation (1/50, 28/50, 32/50)
Neoplastic effects	Adrenal medulla: benign pheochromocytoma (12/50, 17/50, 23/50, 15/48)	None	Adrenal medulla: benign pheochromocytoma (0/50, 4/50, 7/48) Liver: hemangiosarcoma (2/50, 8/50, 10/50)	None
Uncertain findings	None	Adrenal medulla: benign pheochromocytoma (3/50, 7/50, 9/50)	None	None
Decreased incidences	Pancreas: adenoma (12/49, 1/49, 1/49, 0/50); hyperplasia (19/49, 17/49, 8/49, 1/50)	Mammary gland: fibroadenoma (19/50, 10/50, 7/50) Uterus: stromal polyp (13/50, 13/50, 7/50); stromal sarcoma (2/50, 1/50, 0/50); stromal polyp or sarcoma (15/50, 14/50, 7/50)	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pentachloroanisole (continued)

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Positive without S9 in strains TA98 and TA1537 Equivocal with rat S9 in strain TA100 Negative with and without S9 in strains TA100 and TA1535			
L5178Y mouse lymphoma mutations:	Positive with S9			
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:	Positive with and without S9			
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on pentachloroanisole on November 21, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 21, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of pentachloroanisole received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of pentachloroanisole by discussing the rationale for study, describing the experimental design, reporting on the survival and body weight effects, and commenting on compound related neoplasms and nonneoplastic lesions in rats and mice. He reported on pharmacokinetic studies in rats with pentachloroanisole and a major metabolite, pentachlorophenol, and concluded from the results that differences between male and female rats in toxic response to the chemical were not due to differences in absorption or bioavailability. The proposed conclusions were *some evidence of carcinogenic activity* for male F344/N rats, *equivocal evidence of carcinogenic activity* for female F344/N rats, *some evidence of carcinogenic activity* for male $B6C3F_1$ mice and *no evidence of carcinogenic activity* for female $B6C3F_1$ mice.

Dr. R.H. Garman, a principal reviewer, agreed with the proposed conclusions. He asked for clarification of the histomorphologic criteria for diagnostic terminology used in designating malignancy of adrenal medullary lesions.

Dr. L. Zeise, the second principal reviewer, agreed with the proposed conclusions. However, she asked for discussion on whether the level of evidence in female rats should be elevated to *some evidence* based on an incidence of adrenal neoplasms in the 40 mg/kg group. The incidence was above the historical control range and was supported by increased incidences of these neoplasms in male rats and male mice. She suggested that a statement be added to the report indicating that the incidence of pheochromocytomas in 40 mg/kg female rats fell outside that of historical controls. Dr. J. K. Haseman, NIEHS, noted that the increased incidence of adrenal neoplasms in dosed female rats was not significant, reflecting in part that survival in the high-dose groups was increased compared to concurrent and historical control survival rates. Dr. Zeise requested that information on the pharmacokinetic studies be added to the report.

Dr. B. McKnight, the third principal reviewer, agreed with the proposed conclusions for male and female rats and male mice but thought the conclusion for female mice should be changed to *equivocal evidence* based on the dose-related marginally increased incidence of malignant lymphoma supported by a statistically significant trend test. Dr. Irwin commented that since these are common neoplasms, the historical rates are rather variable. The high dose rate, being slightly higher than average, is well within the historical range and therefore not considered to be chemical related. Dr. McKnight said that because the 13 accidental deaths among male rats were indirectly associated with treatment, they should be counted as deaths rather than censored observations. Dr. Haseman said that a second set of survival curves adjusted for the relatively small number of accidental deaths would likely be almost indistinguishable from the first set.

Dr. Garman moved that the Technical Report on pentachloroanisole be accepted with the revisions discussed and with the conclusions as written, *some evidence of carcinogenic activity* for male rats and male mice, *equivocal evidence of carcinogenic activity* for female rats, and *no evidence of carcinogenic activity* for female mice. Dr. D.W. Hayden seconded the motion. Dr. McKnight offered an amendment that the level of evidence for female mice be changed to *equivocal evidence* based on the malignant lymphomas. Dr. Zeise seconded the amendment which was defeated by two yes (Drs. McKnight, Zeise) to eight no votes. The original motion by Dr. Garman was then accepted unanimously with ten votes.